ON HÆMATOPORPHYRIN AS A URINARY PIGMENT IN DISEASE.

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The occurrence of hæmatoporphyrin or of closely allied pigments in the urine, which has been conclusively established by the researches of MacMunn, Neusser, Salkowski, Hammarsten, and other observers, is a phenomenon of great interest, and one to which we may reasonably look to throw important light upon the processes concerned either in the building up or destruction of the colouring matter of the blood.

The study of the occurrence of the pigment in the urine of sufferers from various diseases is one of the paths by which this end may be approached; and the present paper, which embodies the results of the examination of the urine of two hundred individuals, is intended to serve as a contribution to our knowledge of this portion of the subject.

The observations bearing upon the chemical and spectroscopic character of the hæmatoporphyrin found in the cases included in this series, have been already described at considerable length elsewhere.[1] I therefore propose to give in this place only such a brief *résumé* of the conclusions arrived at, as constitutes a necessary introduction to the discussion of the pathological aspects of the question.

Hæmatoporphyrin is an extremely common constituent of the urine, but the amount present is, as a rule, extremely minute. Traces of the pigment, which cannot be detected by precipitation with the neutral and tribasic acetates of lead or with barium chloride and hydrate, according to the processes described by MacMunn and Salkowski respectively, may be found by the addition to the urine of an excess of a 10 per cent. solution of sodium or potassium hydrate, when any hæmatoporphyrin that is present will cling to the precipitate of earthy phosphates which is thrown down, just as hæmatin does in Heller's well-known test for blood pigment. The precipitate is collected upon a filter, and thoroughly washed with distilled water, and afterwards treated with a small quantity of alcohol acidulated with sulphuric acid,

[1] *Journal of Physiology*, vol. xiii., No. 6.

by which means a solution of hæmatoporphyrin, which is almost entirely free from other pigments, is obtained.[1]

Pure acid solutions of urinary hæmatoporphyrin had the same beautiful pink colour as those of hæmatoporphyrin prepared from hæmatin, and the neutral and alkaline solutions were likewise pink. They yielded spectra identical with those of the blood derivative; such slight differences in the positions of the bands as were frequently observed being traced to differences in the solvents, or in the degree of acidity or alkalinity of the solutions.

The acid solutions of the pigment, when free from urobilin, as the extracts from washed soda precipitates always are, showed no band to the less refrangible side of the solar F line, such as MacMunn describes as a constant feature in the spectrum of acid urohæmatoporphyrin. On the other hand, in a few instances, the alkaline spectrum included the extra band in the red, described by the same observer, but this band was also occasionally present in the alkaline spectrum of specimens of hæmatoporphyrin prepared by the sulphuric acid process. On the addition of zinc chloride and ammonia to the solutions no fluorescence was noticed, but a spectrum appeared, identical with that yielded by the blood derivative when similarly treated.

The cases included in the series were not selected on account of any peculiarity of tint of the urine, but rather because they were examples of well-defined or acute diseases. In no instance did the urine present the remarkable claret colour which was observed in most of the recorded cases of hæmatoporphyrinuria.

The observations cover but a very small portion of the field of inquiry, but they serve to bring out certain points which are not without interest.

In one hundred and twenty-six cases the lead or barium method was employed for the detection of the pigment, and in no less than seventy-six of these the absorption bands of acid hæmatoporphyrin were observed when the acidulated alcoholic extracts were examined with the spectroscope, but in twelve cases only was the quantity of pigment present sufficient to yield the complete alkaline spectrum.

The far greater delicacy of the soda method renders the results obtained by its means hardly comparable with the others, and they have therefore been embodied in a separate table. Among the seventy-four cases examined by this method, there were only three in which no trace of hæmatoporphyrin could be detected in the urine; and the complete alkaline spectrum was observed in as many as forty-four of the cases in which the pigment was present.

This much higher proportion of complete observations affords in itself strong evidence that the acid spectrum alone suffices for the recognition of hæmatoporphyrin, but many additional arguments in support of this contention might be brought forward, and especially the fact that, from the specimens which yield the faint acid spectra, the pigment is

[1] Further details will be found in the paper above referred to.

picked out, as hæmatoporphyrin is, by the selective action of the alkaline hydrate and earthy phosphate.

The urine of healthy individuals, when examined by the soda method, was usually found to contain minute traces of hæmatoporphyrin, so minute that the acid bands were only just visible in a concentrated extract, and could sometimes only be seen with a direct vision spectroscope of small dispersive power. Nevertheless, from three such urines, extracts were obtained which, on the addition of ammonia, showed the characteristic alkaline spectrum, so that in these cases, at any rate, the pigment was shown to be of the same nature as that which is frequently present in larger quantities in morbid urines.

In the absence of any method for estimating the amount of hæmatoporphyrin in urine, it will be difficult to convey on paper any very satisfactory notion of the quantities present in the different specimens, although experience enables one to form, in one's own mind at least, a rough estimate of the richness of any particular specimen.

Before proceeding to discuss the results, it will be well to refer to the various conditions under which hæmatoporphyrin or allied pigments have been met with in urine by previous observers.

MacMunn first detected the pigment to which he has assigned the name of urohæmatoporphyrin in the urine of a patient suffering from acute rheumatism, and he afterwards found that it was almost constantly present in that disease. He also met with it in cases of Addison's disease, pericarditis, paroxysmal hæmoglobinuria (between the paroxysms), measles, meningitis, Hodgkin's disease, and enteric fever, and a pigment intermediate between urohæmatoporphyrin and hæmatoporphyrin in a case of exophthalmic goitre.

Le Nobel has found a similar pigment in cases of rheumatism, lobar pneumonia, and cirrhosis hepatis. Neusser found hæmatoporphyrin in the urine of two patients suffering from phthisis pulmonalis and pleurisy respectively; whilst Baumstark obtained a pigment (urorubrohæmatin), presenting considerable resemblances to hæmatoporphyrin, from that of a leprous patient.

In cases recorded by Stockvis, Ranking and Pardington, Salkowski and Hammarsten, pigments closely resembling or identical with hæmatoporphyrin were found in large amounts in the claret-coloured urine of female patients who presented obscure nervous symptoms, or who had recently taken sulphonal in large doses.

The cases embodied in the annexed tables have been arranged under three headings: Firstly, those in which the alcoholic extracts contained enough of the pigment to show both the acid and the alkaline spectra, and in many of which the neutral spectrum, or the spectrum with zinc chloride and ammonia, or both of these, were also observed. In the various cases included in this group the pigment was present in very different amounts, the bands of the alkaline spectrum being in some instances only just visible, whilst in others they were very intense.

Secondly, cases in which the acid spectrum was alone obtained, some of which would doubtless have been included in the previous group had a larger amount of the urine been available for examination.

In the third group are included those cases in which no trace of hæmatoporphyrin could be detected in the urine.

It will be noticed that the cases were not by any means taken at random, but that any promising line of investigation was followed up, as far as the supply of material allowed, with the result that more than half the patients were suffering from one of some six or seven maladies. It is therefore probable that the proportion of cases in which hæmatoporphyrin was found in notable excess is considerably greater than would have been the case if no such selection had been exercised.

It seemed desirable to study not only the occurrence of hæmatoporphyrin in the urine in different diseases, but also the relation of the increased excretion of the pigment to the other morbid phenomena; and accordingly many specimens of the urine were in some cases examined.

The quantities of urine employed varied considerably in different cases, but the majority of the specimens had a volume of some 200 to 400 c.c.

SUMMARY OF THE RESULTS OF THE EXAMINATION OF THE URINE OF 126 INDIVIDUALS FOR HÆMATOPORPHYRIN BY THE LEAD AND BARIUM METHODS.

Diseases.	Total number of Cases.	Acid and Alkaline Spectra obtained.	Acid Spectrum only obtained.	No Hæmatoporphyrin found.	Diseases.	Total number of Cases.	Acid and Alkaline Spectra obtained.	Acid Spectrum only obtained.	No Hæmatoporphyrin found.
Gout,	5	2	2	1	Wasting in a child,	1	0	1	0
Acute and Sub-acute Rheumatism,	23	4	16	3	Emphysema, with Congested Liver,	1	0	1	0
Chorea,	27	2	16	9	Exophthalmic Goitre,	1	0	0	1
Tubercular Affections,	8	2	6	0	Perityphlitis,	1	0	0	1
Lobar Pneumonia,	4	2	0	2	Herpes Zoster,	1	0	0	1
Pleurisy,	6	0	5	1	Broncho-Pneumonia,	1	0	0	1
Cirrhosis Hepatitis,	1	0	0	1	Epilepsy,	2	0	0	2
Enteric Fever,	1	0	1	0	Habit Chorea,	1	0	0	1
Erythema Marginatum,	1	0	1	0	Thrombosis of Veins,	1	0	0	1
Erythema Nodosum,	4	0	2	2	Influenza,	1	0	0	1
Febricula,	1	0	1	0	Asthma,	1	0	0	1
Tonsillitis,	1	0	1	0	Bronchitis,	1	0	0	1
Purpura Simplex,	1	0	1	0	Valvular Disease,	2	0	0	2
Parametritis,	2	0	1	1	Tubal Nephritis,	2	0	0	2
Infantile Paralysis, with Cystitis,	1	0	1	0	Diabetes Mellitus,	2	0	0	2
Empyema,	2	0	1	1	Hemiplegia,	1	0	0	1
Hysteria,	2	0	1	1	Anæmia from Intestinal Hæmorrhage,	1	0	0	1
Chlorosis,	5	0	3	2	Healthy Persons,	8	0	2	6
Albuminuria in a child,	1	0	1	0					
Raynaud's Disease,	1	0	1	0		126	12	65	49

SUMMARY OF THE RESULTS OF THE EXAMINATION OF THE URINE OF 74 INDIVIDUALS, BY THE SODA OR POTASH METHOD.

Diseases.	Total number of Cases.	Acid and Alkaline Spectra obtained.	Acid Spectrum only obtained.	No Hæmatoporphyrin found.	Diseases.	Total number of Cases.	Acid and Alkaline Spectra obtained.	Acid Spectrum only obtained.	No Hæmatoporphyrin found.
Gout, . . .	6	5	1	0	Lead Poisoning, .	1	1	0	0
Acute and Sub-acute Rheumatism, . .	5	4	1	0	Valvular Disease and Congested Liver, .	1	1	0	0
Chorea, . . .	2	1	1	0	Ascites of uncertain origin, . . .	2	0	2	0
Tubercular Affections,	9	6	3	0	General Anasarca of uncertain origin, .	1	1	0	0
Lobar Pneumonia, .	3	2	1	0	Malarial Fever, . .	1	1	0	0
Pleurisy, . . .	4	3	1	0	Tetanus, . . .	1	1	0	0
Cirrhosis Hepatitis, .	3	3	0	0	Peritonitis, . .	1	1	0	0
Erythema Nodosum, .	2	1	1	0	Insane Patients taking Sulphonal, . .	10	5	4	1
Purpura Simplex, .	1	0	1	0	Healthy Persons, .	9	3	4	2
Empyema, . .	1	1	0	0					
Chlorosis, . . .	3	1	2	0		74	44	27	3
Exophthalmic Goitre,	2	0	2	0					
Broncho-Pneumonia, .	1	0	1	0					
Catarrhal Jaundice, .	1	0	1	0	Cases included in the previous Table, .	126	12	65	49
Splenic Anæmia, .	2	1	1	0					
Pernicious Anæmia, .	1	1	0	0					
Paroxysmal Hæmoglobinuria, . . .	1	1	0	0	Totals for entire series,	200	56	92	52

Patients taking Sulphonal.

In view of the observations of Stockvis, Salkowski, and Hammarsten, upon the urine of some patients who had been under treatment with sulphonal, which was found to be very rich in hæmatoporphyrin, an examination of the urine of patients taking that drug promised to yield interesting results. With the kind permission of Dr. Percy Smith, Dr. Belben was good enough to send me specimens passed by ten insane patients who had been so treated in Bethlem Hospital. Of the remaining hundred and ninety patients none had recently taken sulphonal.

With two exceptions the urines presented no peculiarity as to tint, but in two instances it was high-coloured and red, although the amount of hæmatoporphyrin present was small. In no instance was the pigment found in larger quantity than is often present in the urine of gouty or rheumatic patients.

The urine of a man, aged forty-one, who was suffering from general paralysis, and who had taken no sulphonal, was found to contain a small amount of hæmatoporphyrin, sufficient to yield a faint alkaline spectrum; ten days later no increase could be detected, although the patient had taken thirty grain doses of sulphonal every night in the interval. In the urine of another male patient, aged thirty-nine, suffering from acute melancholia, and who had taken thirty grain doses nightly for ten days,

no hæmatoporphyrin could be detected either by the sodium or barium method. In the two other male cases, a considerable amount and a mere trace were found respectively.

Of the six female patients, three were excreting the pigment in considerable, and the others in very small amounts. One of these patients, who was a sufferer from delusional insanity, had taken twenty grains of sulphonal every evening for months, whilst another had been taking thirty grain doses for six weeks.

The above results seem to show conclusively that excessive hæmatoporphyrinuria is not a constant result of the administration of sulphonal, although it seems hardly possible to doubt that, under exceptional circumstances, the appearance of very large quantities of hæmatoporphyrin in the urine is attributable to this treatment.

Gout.

Of the diseases included in the series, gout is that in which the largest amounts of hæmatoporphyrin were most commonly met with in the urine. In only one case was none found on either of the occasions on which the urine was examined by the lead acetate method. In this instance there could be no question as to the diagnosis, for the patient was suffering from a sub-acute exacerbation of the chronic disease, and presented very large tophaceous deposits upon the backs of the hands, and in other situations.

In two cases chronic lead poisoning appeared to have played an important part in the causation of the gouty condition.

Sometimes the quantity of hæmatoporphyrin present in the urine underwent a rapid diminution as the acute attack for which the patient applied for treatment subsided; but in other instances the excessive excretion long outlasted the acute stage. One man, who had signs of renal gravel in addition to his articular troubles, and who occasionally passed a little blood, remained under observation for several months, and on each of the fifteen occasions on which the urine was examined hæmatoporphyrin was found to be present in relatively large amount. In another instance a similar excess was observed at each of the two observations which were separated by an interval of about two months.

The amount of the pigment found in the various cases did not appear to stand in any definite relation to the severity of the attacks, or to the number of articulations involved.

Acute and Sub-acute Rheumatism.

This is the disease in which MacMunn originally found urohæmatoporphyrin, and he pointed out that it is almost constantly present in the urine of those who suffer from acute rheumatism.

In nearly all the cases (twenty-five out of twenty-eight) of acute and

sub-acute rheumatism included in the series, hæmatoporphyrin was present in quantities sufficient to allow of its detection by any method, but, as a rule, the amounts were not equal to those met with in the gouty cases.

The richness of the urine in hæmatoporphyrin did not appear to stand in any direct relation to the severity of the attacks, the largest quantities being often found in quite sub-acute cases, whereas in very acute cases mere traces were sometimes present.

Neither in this nor in other diseases did the sex or age of the patient exercise any appreciable influence.

As a rule the excess tended to disappear when convalescence was established, but sometimes, as in the gouty cases, the pigment continued to be excreted in undiminished amounts. This was especially noticeable in the case of one patient who, before many weeks had elapsed, was readmitted to the hospital with a relapse.

That the salicylic treatment, which is now so generally employed in these cases, is not responsible for the excess of hæmatoporphyrin in the urine is shown by the fact that in some instances the excessive amounts were found in urine passed immediately after their admission to the hospital by patients who said that they had had no treatment, and whose urine failed to give the characteristic reaction with ferric chloride.

In a paper read before the Royal Medical and Chirurgical Society the results of simultaneous examinations of the blood and urine of eight patients suffering from rheumatic fever were included, and I there showed that no relation could be traced between the changes in the number and worth of the red corpuscles, and the appearance and disappearance of hæmatoporphyrinuria. It may be that the methods employed were not sufficiently delicate to detect a relation which may nevertheless exist. I hope to continue the work along these lines, examining only the blood of those patients who may be excreting unusually large amounts of the pigment.

Chorea.

It is difficult to estimate how much importance may be attached to the results obtained in the choreic cases. It is true that chorea is one of the few diseases in which large quantities of hæmatoporphyrin were sometimes found in the urine, but similar results might perhaps have been obtained in other disorders if an equally large number of cases had been examined.

As a rule the amount present was sufficient to allow of its ready detection by any method, and in only two cases out of the twenty-nine was the soda method employed. It may therefore be conceded that an increased excretion of hæmatoporphyrin is a fairly constant phenomenon in chorea.[1]

[1] Some of these results were embodied in a preliminary note in the *Lancet*, 1892, i., p. 793.

It will be seen, moreover, that the increase was most frequently observed in cases in which there was reason to suspect a rheumatic element, although in one of the cases in which the amount was greatest there was neither family nor personal history of rheumatism, nor was the heart affected.

	Total Number of Cases.	Acid and Alkaline Spectra obtained.	Acid Spectrum only obtained.	No Hæmatoporphyrin found.
Cases with personal histories of articular rheumatism, .	9	1	8	0
Cases with doubtful rheumatic personal histories, . .	3	1	1	1
Cases with cardiac murmurs only, ...	3	0	3	0
Cases with rheumatic family histories only, . . .	3	0	1	2
Cases with no indications of rheumatic origin, . .	11	1	4	6
Totals, .	29	3	17	9

Tubercular Affections.

An excessive excretion of hæmatoporphyrin was found to be very constant in tubercular cases, whatever the seat of the disease. The cases included under this head embraced examples of general tuberculosis, pulmonary phthisis, peritonitis, and tubercular joint disease.

In the single example of general tuberculosis the quantity present was less than in most of the more chronic forms, but it underwent a great increase on the day preceding the death of the patient.

The maximum quantity was found in the urine of a patient suffering from advanced phthisis who had, in addition, acute hepatic congestion.

It will be remembered that one of Neusser's patients was phthisical, and that MacMunn has met with an excess of urohæmatoporphyrin in Addison's disease.

Lobar Pneumonia.

Le Nobel has met with a pigment resembling hæmatoporphyrin in the urine of patients with acute pneumonia, and in a number of my cases the pigment was present in considerable amounts. On the other hand, in some few cases little or none was found. The observations were made upon specimens of urine passed either during the febrile period, or very shortly after the crisis.

Pleurisy.

In nine out of ten cases of pleurisy, hæmatoporphyrin was found in the urine in moderate but never in unusually large amounts, the one

exception being the only case in which the affection had not passed beyond the dry stage. In only one of the three additional cases of empyema was the quantity present at all large.

Diseases attended with profound Anæmia.

Although the examples of such conditions included in the tables are few in number, the results arrived at were of considerable interest.

It might be expected that in cases of profound anæmia the blood pigment would be largely excreted in the form of hæmatoporphyrin, but this did not appear to be the case, whereas the amount of urobilin present was in some instances very great.

The tables fail to convey a correct impression upon this point, because most of these cases were examined by the soda method, which so readily permits of the observation of the alkaline spectrum.

In the cases of chlorosis the urine was, as a rule, pale and comparatively poor in pigments of all kinds; in none of them was there any excessive excretion of urobilin. The specimens were, when possible, obtained before treatment with iron was commenced. In no instance was any large amount of hæmatoporphyrin found.

The barium method failed to detect any of the pigment in the urine of a man who was rendered extremely anæmic by repeated intestinal hæmorrhages of doubtful origin, but its absence in such a case goes for nothing.

In a case of pernicious anæmia the urine was high-coloured, and contained much pathological urobilin, but the hæmatoporphyrin was scanty.

Of two children with severe splenic anæmia one passed urine containing much urobilin, and no more hæmatoporphyrin than is usually present in health; but the urine of the other child, who was older, contained much uroerythrin and pathological urobilin, and in addition an amount of hæmatoporphyrin comparable with that found in the richest cases of the series.

Hepatic Diseases.

The urine of patients suffering from hepatic diseases is apt to be rich in pigments, not only the bile pigment but also large amounts of pathological urobilin and urocrythrin being frequently found, whilst in some cases there is in addition a noteworthy excess of hæmatoporphyrin. The cases included in the series are too few to supply any basis for generalisation, but they serve to confirm Le Nobel's observation as to the presence of a hæmatoporphyrin pigment in the urine of patients with cirrhosis. It will be seen from the annexed table that in one case of cirrhosis none was found, but there was a large amount of pathological urobilin present which may have concealed its presence. When the

soda method was employed the urobilin was entirely removed by washing the precipitate, and did not therefore interfere at all with the observations.

Sex and Age of Patient.	Nature of the Disease.	Methods employed.	Observations.
1. Female, 2 years.	Catarrhal Jaundice.	Soda.	Pathological urobilin and uroerythrin present. The acidulated extract showed the bands of acid hæmatoporphyrin faintly.
2. Male, 44 ,,	Cirrhosis Hepatitis.	Lead.	Much pathological urobilin; no hæmatoporphyrin found.
3. Male, 64 ,,	,, ,,	Barium and Soda.	Much urobilin; and an unusually large amount of hæmatoporphyrin; all the spectra of this pigment were observed.
4. Male, 40 ,,	,, ,,	Soda.	Much urobilin; much hæmatoporphyrin also present.
5. Male, 29 ,,	,, ,,	Soda.	Much less hæmatoporphyrin than in previous cases, but still a considerable amount.
6. Male, ,,	Emphysema—Tricuspid Regurgitation. Congested Liver.	Lead and Barium.	Pathological urobilin present, and a small quantity of hæmatoporphyrin.
7. Male, 9½ ,,	Valvular Disease and Congested Liver.	Soda.	Pathological urobilin, and a small quantity of hæmatoporphyrin.
8. Male, 37 ,,	Acute Hepatic Congestion—Phthisis.	Barium.	Much hæmatoporphyrin present.

Isolated Cases of Interest.

The richest in hæmatoporphyrin of all the urines examined was that of a man who was suffering from general anasarca, for which no satisfactory explanation was forthcoming. Nothing abnormal could be detected in his chest, and the urine was quite free from proteids.

As in a case recorded by MacMunn, hæmatoporphyrin was found in considerable quantity in the urine of a patient suffering from paroxysmal hæmoglobinuria, in the intervals between the paroxysms, and in this as in the previous case all four characteristic hæmatoporphyrin spectra were observed.

Typhoid fever having been unusually scarce during the past year, in the hospitals from which the specimens were obtained, only a single case is included in the series. It would have been interesting to have examined a number of cases of this disease, which is one of those in which MacMunn found urohæmatoporphyrin in the urine.

In the only case of tetanus in which the urine was examined the pigment was found to be present in moderately large amount.

It must be admitted that the results of the study of the above series of cases are somewhat disappointing, since they throw but little light upon the origin of urinary hæmatoporphyrin; whilst the very wide distribution of the pigment in disease deprives its occurrence of all real diagnostic value. Nevertheless the observations serve to bring out the following points:—

1. That hæmatoporphyrin is an almost constant constituent of the urine both in health and in disease, a large excess being present under a variety of morbid conditions.

2. That the diseases in which the greatest increase is observed are for the most part systemic maladies, some of which belong to the infective group, whilst to others such an origin can hardly be attributed.

3. That in acute diseases the increased excretion of hæmatoporphyrin stands in no direct relation to the severity of the attack, to the amount of febrile disturbance, or to the intensity of the local manifestations.

4. That in diseases attended with extreme anæmia there is no such constant increase of the urinary hæmatoporphyrin as might be expected, if the destroyed hæmoglobin were excreted in this form.

5. That in some cases of hepatic disease a large excess of the pigment is present in the urine.

In concluding this paper I must not omit to thank those who by kindly allowing me to examine the urine of patients under their care have rendered the work possible, namely, Dr. Andrew and Sir Dyce Duckworth, Drs. Sturges, Barlow, and Hadden; my colleagues, Drs. Donald Hood, Drewitt, and Herringham; and lastly, Dr. Percy Smith and Dr. Belben, who have supplied me with specimens from Bethlem Royal Hospital.